REMARKS/ARGUMENTS

Claims 1, 3-5, 13, 16-19, 22, and 33-34 are pending in this application and presented for examination. Claims 2, 8 and 35-40 have been canceled without prejudice or disclaimer. Claims 1, 3-5, 13, 19 and 33 have been amended. No new matter has been introduced with the foregoing amendments. Reconsideration is respectfully requested.

Applicants gratefully acknowledge the withdrawals of rejections under 35 U.S.C. §112, first paragraph; 35 U.S.C. §102(a); and 35 U.S.C. §103(a).

I. FORMALITIES

Claims 1, 13 and 19 have been amended to clarify that "the low dose does not induce substantial tolerance". Support for the amendment to the claims is found, for example, on page 15, line 8. Further, claim 1 has been amended to set forth that the cells are in a subject. Support for such amendment is found for example, in claim 2.

Claim 33 has been amended to clarify that "the low dose is 3 to 10,000 fold lower than a dose of the nitric oxide mimetic that produces vasodilation". Support for the amendment is found, for example, on page 11, line 33 bridging to page 12, line 5. Thus, no new matter has been introduced. As such, Applicants respectfully request that the amendments to the claims be entered.

II. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-5, 8, 13, 16-19, 22 and 33-40 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Office Action indicates that amended claims 1-5, 8, 13, 16-19 and 22 recite or read on "low dose is 3 to 10,000 fold lower than a dose of said nitric oxide mimetic that produces vasodilation". The Examiner considers this a somewhat indefinite claim feature primarily because of the term "vasodilation". The Examiner argues that vasodilation is widening of the lumen of any blood vessel and since blood vessels supply blood to tumor cells, the claim feature is allegedly indefinite. To the extent the

rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

In order to expedite prosecution, Applicants have amended claims 1, 13 and 19 to specify that "the low dose does not induce substantial tolerance". Basis for this amendment is supported on page 15, line 8, where it is stated that the invention is concerned with "**achieving the ultimate goal of increasing, restoring or maintaining nitric oxide mimetic activity of cells so that a malignant phenotype is prevented or inhibited without substantial drug tolerance to the NO mimetic developing and without unwanted side effects**". By further specifying that no substantial tolerance is induced by use of the mimetic, the claim has been further defined. As such, Applicants assert that the claims are clear and definite.

For example, as set forth on page 11, line 24 bridging to page 12, line 5 of the specification:

> "[I]t is known that administration of nitric oxide or compounds which deliver nitric oxide to human beings at doses **conventionally employed to treat cardiovascular conditions (*i.e.*, GTN at 0.2 mg/h or greater) by vasodilation can provoke powerful vasodilator responses as well as development of drug tolerance against GTN upon repeated administration**. Such administration is often accompanied by a number of undesirable side effects including headache, flushing and hypotension. In contrast, preferred doses of nitric oxide mimetic administered in the present invention to inhibit and prevent a malignant cell phenotype are lower, preferably at least 3 to 10,000-fold lower, more preferably at least 100- to at least 10,000-fold lower than those typically used in other therapeutic applications such as vasodilation and thus do not induce tolerance to the NO mimetic as quickly nor undesirable side effects."

Furthermore, the specification indicates on page 11, lines 25-35, that the administration of nitric oxide at **doses conventionally employed to treat cardiovascular conditions by vasodilation can provoke powerful vasodilator responses as well as drug tolerances and undesirable side effects**.

In contrast, the doses of nitric oxide mimetic administered in the instant invention to inhibit and prevent a malignant cell phenotype are lower, in fact, preferably 3 to 10,000-fold lower than those used in other applications such as vasodilation and, thus, do not induce tolerance to the NO mimetic as quickly nor undesirable side effects (please see page 12, lines 1-

5). Besides specifying that the low dose does not induce tolerance, Applicants have established a clear comparison. Specifically, by comparing the administration of the nitric oxide mimetic for use in inhibiting a malignant cell phenotype with the administration of nitric oxide for use in vasodilation, Applicants have established a comparative scale, *i.e.,* wherein a 3 to 10,000-fold lower dose is employed in the instant invention.

With respect to the term "vasodilation" it is stated that a skilled person will appreciate that "vasodilation" refers to a systemic effect known in the art (*e.g.,* a lowering of blood pressure). As previously discussed (shown in Table 1, pages 13-14 of the specification), for nitric oxide mimetics conventionally used to alter properties in the circulatory system (*e.g.,* systemic indications such as treating congestive heart failure, angina pectoris, hypertension, and the like), a low dose according to the present invention is less than the amount for such systemic conventional use. In addition, one of ordinary skill in the art would know of routine methods for the determination of a minimum dose of any nitric oxide mimetic required to significantly decrease the mean arterial pressure (*i.e.,* produce vasodilation), which could then be used to calculate the low dose for a particular nitric oxide mimetic for use in the present invention.

Therefore, the term "vasodilation" is not indefinite in light of the extensive disclosure within the specification. As such, one of ordinary skill in the art would know, or easily be able to ascertain, the meaning of vasodilation in the instant invention based on methods well-known in the art and the teachings of the specification. Therefore, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. §112, second paragraph rejection.

The Office Action further indicates that claims 33-40 recite doses, wherein the unit of the dose is "M", meaning moles per liter. The recited concentration is allegedly an incomplete description of the "dose" because the dose will depend on how much of the, for example, 10^{-14} M solution is given to a patient. The Examiner suggests incorporation of the "3 to 10,000-fold lower" feature of claim 1, in addition to the concentration feature.

In order to expedite prosecution, Applicants have amended the claims according to the Examiner's suggestions. In light of this amendment, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph, be withdrawn.

III. FIRST REJECTION UNDER 35 U.S.C. § 102(b)

Claims 1, 4-5 and 8 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Ushmorov *et al.* (*Blood, J. of the American Society of Hematology* (1999), 93:2342-2352). The Office Action asserts that Ushmorov *et al.* disclose treating human leukemia T-cell lines with $2x10^{-4}$ M GTN and that 33% apoptosis is obtained. The Office Action further alleges that effective treatment of leukemia patients by using NO donors or other agents to induce apoptosis through damage of mitochondrial functions in leukemic cells is disclosed. The Examiner asserts that claims 1, 4, 5 and 8 are readable on *in vitro* methods and that the "low dose is 3 to 10,000-fold lower than a dose of a nitric oxide mimetic that produces vasodilation" feature has no material weight in an *in vitro* method since *in vitro* leukemic cell samples would not manifest vasodilation. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

In order to expedite prosecution, Applicants have amended claims 1 and 8 to set forth that the cells are in a subject, such as a human being. Thus, the claims are drawn to *in vivo* methods. In view of the amendments, Applicants respectfully request that the rejection of claims 1, and 4-5, under 35 U.S.C. §102(b) be withdrawn.

IV. SECOND REJECTION UNDER 35 U.S.C. § 102(b)

Claims 1-5, 8, 13, 16-18 and 19 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Derwent abstract Accession Number 1998-313779 (abstracting DE 19732323).

The Office Action alleges that the cited reference explicitly discloses a local application of nitroglycerin, *i.e.,* directly onto the tumor. The Examiner asserts that such local administration would not produce vasodilation outside of the locally administered area such as a targeted tumor mass and to the extent that vasodilation applies to systemic or coronary vasodilation, *i.e.,* it does not apply to vasodilation of tumor blood vessels, the claim feature is allegedly met. The Examiner contends that the cited reference administers the nitroglycerin plus cancer drug to subjects with cancer, and thus such subjects allegedly satisfy "at risk for or

suffering from a malignant cell phenotype". To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

"Anticipation requires identity of invention. The claimed invention, as described in appropriately construed claims, must be the same as that of the reference in order to anticipate." *Glaverbel Societe Anonyme v. Northlake Marketing & Supply Inc.*, 45 F.3d 1550, 33 USPQ.2d 1496, 1498 (Fed. Cir. 1995).

The abstract discloses a *combination* of a blood flow promoting medicament and microspheres. The blood flow promoting medicament provides a detectable elevated concentration of technetium-99m (the most widely used radioisotope for diagnosing diseased organs) in selected organs and tissue regions and it is homogenously mixed with nitroglycerin and then combined with the microspheres. The medicament is then administered arterially or locally for selective treatment of diseased regions. Specifically, the medicament is administered arterially or locally to provide *higher* concentrations than obtained in systemic therapy. The advantage of this system (medicament + microspheres + nitroglycerin) allows a reduction of the dose of the medicament.

The instant invention does not employ microspheres nor does the instant invention employ a nitric oxide mimetic in order to homogenously *mix* it with another substance or medicament.

Rather, the instant invention uses a low dose of NO mimetic, wherein the low dose is 3 to 10,000 fold lower than a dose that produces vasodilation. Furthermore, the instant invention is not administered arterially or locally to provide a *higher* concentration of the mimetic (compared to systemic therapy).

As the Examiner must certainly be aware, "[w]hen a claimed invention is not identically disclosed in a reference, and instead requires picking and choosing among a number of different options disclosed by the reference, then the reference does not anticipate." *Mendenhall v. Astec Industries, Inc.*, 13 USPQ.2d 1913, 1928 (Tenn. 1988), aff'd, 13 USPQ.2d 1956 (Fed. Cir. 1989).

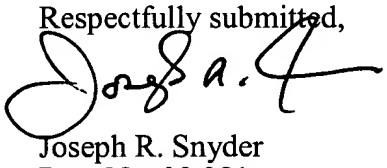
Clearly, the abstract does not teach or even suggest the use of a nitric oxide mimetic for the treatment of cancer. In light of this amendment, Applicants respectfully request that the rejection of claims under 35 U.S.C. §102(b) be withdrawn.

V. CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The Examiner is respectfully requested to send this application to issue.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Joseph R. Snyder
Reg. No. 39,381

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300
JS:js
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